# Low-Dose Aspirin Use Does Not Increase Survival in 2 Independent Population-Based Cohorts of Patients With Esophageal or Gastric Cancer

Spence, A., Busby, J., Johnston, B., Baron, J. A., Hughes, C., Coleman, H., & Cardwell, C. (2017). Low-Dose Aspirin Use Does Not Increase Survival in 2 Independent Population-Based Cohorts of Patients With Esophageal or Gastric Cancer. *Gastroenterology*, *154*(4), 849-860. https://doi.org/10.1053/j.gastro.2017.10.044

**Published in:**
Gastroenterology

**Document Version:**
Peer reviewed version

**Queen's University Belfast - Research Portal:**
Link to publication record in Queen's University Belfast Research Portal

**Title**

Low-dose Aspirin was Not Associated with Improved Survival among Patients with Esophageal or Gastric Cancer in Two Population-based Cohorts

**Short title**

Aspirin and gastroesophageal cancer survival

**Authors**

**Dr Andrew D Spence[a], Dr John Busby[a]**, Professor Brian T Johnston[b], Professor John A Baron[c], Dr Carmel M Hughes[d], Dr Helen G Coleman[a], Dr Chris R Cardwell[a]

**Authors' affiliations**

[a]Cancer Epidemiology and Health Services Research Group, Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, United Kingdom

[b]Belfast Health and Social Care Trust, Belfast, Northern Ireland, United Kingdom

[c]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC.

[d]School of Pharmacy, Clinical and Practice Research Group, Queen's University Belfast

**Grant support**

This work was supported by a Clinical Research Bursary from Cancer Research-UK [C54914/A20558]. The published study protocol was approved by The Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency Database Research (protocol number: 15_096RMn3)

Correspondence to: Dr Andrew Spence MSc, MRCP, Gastroenterologist, Institute of Clinical Sciences Block B, Queen's University Belfast, Royal Victoria Hospital, Belfast, Northern Ireland, BT12 6BA.

Telephone: +44 (0) 28 9063 5009

Fax: +44 (0) 28 90235900

Email: aspence04@qub.ac.uk

**Disclosures**

The authors have nothing to disclose

**Author contributions**

ADS, CRC and CMH conceived and designed the study. ADS, CRC, HGC, BTJ and CMH were involved in data acquisition. ADS, CRC and BTJ obtained funding for the study. JB and CRC conducted statistical analysis. ADS, JB, JAB and CRC contributed to interpretation of data. BTJ and HGC acted as study supervisors. JAB, BTJ and HGC critically revised the manuscript for important intellectual content. ADS and CRC drafted the manuscript and all co-authors contributed to and agreed the final manuscript.

**ABSTRACT**

**Background & Aims**: Pre-clinical studies have shown aspirin to have anti-cancer properties and epidemiologic studies have associated aspirin use with longer survival times of patients with cancer. We studied 2 large cohorts to determine the association between aspirin use and cancer-specific mortality in patients with esophageal or gastric cancer.

**Methods**: We performed a population-based study using cohorts of patients newly diagnosed with esophageal or gastric cancer, identified from cancer registries in England from 1998 through 2012 and the Scottish Cancer Registry from 2009 through 2012. Low-dose aspirin prescriptions were identified from linkages to the United Kingdom Clinical Research Practice Datalink in England and the Prescribing Information System in Scotland. Deaths were identified from linkage to national mortality records, with follow up until September 2015 in England and January 2015 in Scotland. Time-dependent Cox regression models were used to calculate hazard ratios (HR) and 95% CIs for cancer-specific mortality by low-dose aspirin use after adjusting for potential confounders. Meta-analysis was used to pool results across the two cohorts.

**Results**: The combined English and Scottish cohorts contained 4654 esophageal cancer and 3833 gastric cancer patients including 3240 and 2392 cancer-specific deaths, respectively. The proportions surviving 1 year, based upon cancer-specific mortality, were similar in aspirin users vs non-users after diagnosis with esophageal cancer (48% vs 50% in England and 49% vs 46% in Scotland, respectively) or gastric cancer (58% vs 57% in England and 59% vs 55% in Scotland, respectively). There

was no association between post-diagnosis use of low-dose aspirin and cancer-specific mortality among patients with esophageal cancer (pooled adjusted HR, 0.98; 95% CI, 0.89–1.09) or gastric cancer (pooled adjusted HR, 0.96, 95% CI, 0.85–1.08). Long-term aspirin use was not associated with cancer-specific mortality after diagnosis of esophageal cancer (pooled adjusted HR, 1.03; 95% CI, 0.85–1.25) or gastric cancer (pooled adjusted HR, 1.06; 95% CI, 0.85–1.32).

**Conclusions:** In analyses of 2 large independent cohorts in the United Kingdom, low-dose aspirin usage was not associated with increased survival of patients diagnosed with esophageal or gastric cancer.

**KEY WORDS**: esophagus, stomach; anti-platelet; drug; risk factor

**Word count**

Abstract: 337

Main text: 5,333

## Introduction

Gastric and esophageal cancer are the third and eighth most common cancers worldwide, comprising 6.8% and 3.2% of total cancer incidence, respectively.[1] These cancers have poor prognosis (with 5 year survival rates of gastric cancer of 29% and esophageal cancer of 20%),[2] highlighting the need for additional treatment options.

Aspirin is used as an analgesic at high doses, and as an anti-platelet to prevent cardiovascular disease at low-doses (usually around 75mg).[3] Platelets play an important role in cancer growth and metastasis[4-6] and aspirin has been shown to prevent experimentally induced metastases in mice.[7] In humans, long term follow-up of randomised controlled trials of aspirin to prevent vascular events, have shown a 50% reduction in cancer-specific death in esophageal and gastric cancer patients on aspirin,[8] and a 60% reduction in the risk of metastases in non-colorectal gastrointestinal cancer patients on aspirin.[9] These protective effects were observed regardless of aspirin dose but were only observed for adenocarcinomas.[8;9] However, as these patients were taking aspirin prior to esophageal or gastric cancer diagnosis it remains unclear whether low-dose aspirin use after cancer diagnosis, a time point more relevant for clinical intervention, confers any benefit. Furthermore, a more recent meta-analysis by the United States Preventive Services Task Force concluded that the effect of aspirin on cancer mortality was not clearly established.[10]

Unfortunately, there have not been any epidemiological studies that have investigated the association between low-dose aspirin use after diagnosis of gastric or esophageal cancer and cancer-specific mortality. Three independent studies[11-13] have reported

marked protective effects of aspirin on all-cause mortality in gastric and esophageal cancer patients, but these associations could reflect non-cancer mortality. Furthermore, in two studies these associations were restricted to subgroups of esophageal cancer patients[12] and esophageal squamous cell carcinoma patients,[13] and in the third study,[11] the associations were attenuated when methods to reduce immortal time bias were employed. Further evidence on the impact of low-dose aspirin use in patients with esophageal or gastric cancer is required to inform the decision to start trials, and inform the conduct of ongoing trials.[14]

Using two independent population-based datasets, we investigated the association between low-dose aspirin use and cancer-specific mortality in patients with esophageal or gastric cancer.

## Materials & methods

### Data sources

*England:* The English data were based upon the UK Clinical Practice Research Datalink (CPRD), linked with the Office for National Statistics (ONS) and National Cancer Data Repository (NCDR). The NCDR contains data on all patients identified in all English cancer registries, including date and site of primary cancer diagnosis, tumor prognostic features (e.g. stage, grade, morphology) and treatment data. The CPRD is the largest computerized database of its kind in the world. CPRD encompasses approximately 6% of the UK population and is broadly representative in terms of age, sex, ethnicity and body mass index (BMI).[15] The CPRD contains information including patients' diagnoses, demographics, medication prescriptions and comorbidities. The ONS death data for the UK contains information on the causes and dates of death. Linkages of the databases were conducted using the NHS number, date of birth, gender and postcode of each patient. As linkage involved the English NCDR, only patients registered in English GP practices were included in this study. Ethical approval for research using CPRD data has been obtained from a multicentre research ethics committee. The study protocol was approved by The Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency Database Research (protocol number: 15_096RMn3) and was made available to reviewers.

*Scotland*: The Scotland data utilised linkages between national datasets including the Scottish Cancer Registry (SMR06), the Prescribing Information System, the General / Acute Inpatient and Day Case dataset (SMR01), the Outpatient Attendance dataset

(SMR00) and the National Records of Scotland Death Records, covering the entire population of Scotland. Created in 1958, the Scottish Cancer Registry captures information on all cancers occurring in Scotland, including date and site of primary cancer diagnosis, grade and treatment data. The Prescribing Information System holds records regarding all medicines dispensed in the community for the entire population of Scotland. The General / Acute Inpatient and Day Case dataset contains information on hospital diagnoses and operations, and the Outpatient Attendance dataset contains diagnoses and medical procedures from new and follow up appointments at outpatient clinics. The National Records of Scotland Death Records contain date and cause of death. Linkages between data sources were conducted using the Community Health Index number (a unique number to individuals in Scotland). The study was approved by the Privacy Advisory Committee of the National Health Service (NHS) National Services Scotland.

Study design

A cohort of individuals newly diagnosed with esophageal or gastric cancer (ICD codes C15 to C16, respectively) in England between 1998 and 2012, and in Scotland between 2009 and 2012 was identified from cancer registries. Patients with previous cancer diagnosis apart from non-melanoma skin cancer and in-situ tumors, were excluded from the cohort. Esophageal and gastric cancer-specific and all-cause deaths were identified from ONS records in England (available up to September 2015) and National Records of Scotland Death Records in Scotland (available up to January 2015). Esophageal and gastric cancer-specific deaths were defined as those with underlying cause of death ICD codes C15, C16 or C26 (‘other and ill-defined digestive organs’ included as it seems unlikely that patients diagnosed with gastric or

esophageal cancer would die from an unrelated digestive organ cancer). In analyses of esophageal and gastric cancer-specific mortality, patients were censored at the time of death from other causes or end of follow-up. Patients who died within the first six months after diagnosis of esophageal or gastric cancer were excluded from the analysis as it is unlikely post-diagnosis low-dose aspirin medication use would impact their prognosis. Thus, the accrual of person years at risk began six months after esophageal or gastric cancer diagnosis. Patients were followed up to the end of registration with the general practice, last date of data collection from general practice, date of death or end of ONS follow-up in England (30th September 2015) or the date they left Scotland or end of follow up in Scotland (1st January 2015).

Exposure

Low-dose aspirin (75 mg) use was identified from prescriptions within England from the CPRD and dispensed medications within Scotland from the Prescribing Information System. A quantity of 28 tablets was assumed for the less than 2% of prescriptions for which quantity was assumed incorrect (if less than seven or greater than 365), as this is the most common number of tablets in a prescription. One tablet of low-dose aspirin daily was assumed to be taken daily, as this has been designated to be the defined daily dose (DDD), by the World Health Organisation classification.[16] High dose aspirin comprised less than 2% of total aspirin prescriptions, during the exposure period in England and Scotland, and was ignored in all analyses.

## Confounders

Data on histology (including esophageal adenocarcinoma and squamous cell carcinoma), grade and treatment (radiotherapy, chemotherapy or surgery) within six months of diagnosis were retrieved from cancer registries in England (from NCDR) and the Scottish Cancer Registry. The following comorbidities were identified: acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebrovascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes and renal disease. In England these comorbidities were identified from GP records before cancer diagnosis (based upon an average of 7.7 years of available records using a previously developed Read code list[17]). In Scotland these comorbidities were identified from hospital inpatient and outpatient clinic data available from 1999 (using a previously developed ICD code list[18]). Statin use was determined from medication data as described above. Deprivation level was determined from postcode of residence in England using the English Index of Multiple Deprivation, and in Scotland based upon postcode of residence using the 2009 Scottish Index of Multiple Deprivation.[19] Smoking status (categorised as current, ex or never) and BMI were available from GP diagnosis codes prior to cancer diagnosis within the CPRD cohort; records older than 10 years were discarded.

## Statistical analysis

Time-varying Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CI) for cancer-specific mortality comparing aspirin users to non-users in esophageal and gastric cancer sites. In the main analysis low-dose aspirin use from the date of diagnosis was considered a time varying covariate[20] with patients classified as non-users until 6 months after their first prescription at

which point they became users until the end of follow-up. Using such a lag is recommended,[21] as low-dose aspirin is unlikely to have an immediate effect on cancer progression. A diagram illustrating this design is shown in Supplementary Figure 1. The main model included the following variables: sex, age, year of diagnosis, deprivation (defined above, in fifths), cancer treatment within 6 months (using separate variables for radiotherapy, chemotherapy and surgery), comorbidities prior to diagnosis (using separate variables for acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebrovascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes and renal disease) and statin and aspirin use (as time varying covariates, as defined above).

Exposure-response analyses for duration of aspirin use were undertaken using a time-varying covariate with patients deemed non-users until 6 months after their first prescription, a short term user between 6 months after their first prescription and 6 months after their 365$^{th}$ tablet and a long term user after this time. Similar analyses were also conducted for different total amounts of low-dose aspirin use (182, 365, 548 and 730 tablets). Tests for trend were calculated, within the regression models using Wald tests, based upon the estimated HR per category increase of aspirin use. Separate analyses were conducted within esophageal cancer cases by histology (adenocarcinoma and squamous cell carcinoma) and for adenocarcinoma in gastric cancer patients. Summary HRs and standard errors from England and Scotland were combined using fixed effects models to calculate pooled HRs.[22] The probabilities of survival at 1 year after the start of follow-up was estimated in aspirin users and non-users, based upon cancer-specific mortality in Kaplan-Meier curves plotted using the Simon and Makuch method to account for aspirin as a time varying covariate.[23] All

analyses were conducted using STATA 14 (StataCorp, College Station, TX, USA) statistical analysis software.

Sensitivity analyses were conducted with a lag of zero years (in which the accrual of person years at risk began at diagnosis, and all deaths after diagnosis were included), a lag of 3 months (in which the accrual of person years at risk began at 3 months, and deaths in the first 3 months were excluded) and a lag of 1 year (in which the accrual of person years at risk began from 1 year after diagnosis, and deaths in the first year after diagnosis were excluded), see Supplementary Figure 1 for an illustration. Two simplified analyses, which control for immortal time bias without using time-varying covariates,[20] were conducted. First, aspirin exposure was based on any use in the year prior to diagnosis (in which the accrual of person years at risk began at diagnosis, and all deaths after diagnosis were included). Second, aspirin exposure was based on any use during the six months after diagnosis and the accrual of person years at risk began six months after diagnosis. Additional analyses were conducted comparing aspirin users with non-users after restricting each cohort to patients who did not use aspirin in the year prior to cancer diagnosis, and conversely those who were aspirin users prior to cancer diagnosis. Further analyses were also conducted comparing aspirin users with non-users after diagnosis adjusting for aspirin use in the year prior to diagnosis and comparing aspirin users with non-users after diagnosis stratifying by statin use during that time period. A separate analysis was also conducted additionally adjusting for tumor grade as well as an analysis restricted to patients treated with surgery, a more homogeneous cohort of lower stage patients. Analyses were repeated for all-cause mortality outcomes.

Further adjustments were possible in the English data only, in which cancer stage, smoking and BMI were available. We performed additional sensitivity analysis adjusting for tumor prognostic features (stage, grade) and patient lifestyle factors (smoking, alcohol consumption, obesity) using complete-case and multiple imputation with chained equations (MICE). The MICE imputation used ordered logit models with age, deprivation, death indicator and the baseline hazard function as covariates.[24] Briefly, MICE is a simulation-based approach for handling missing data which leads to valid statistical inferences under certain circumstances.[25]

For comparison with a previous study,[12;26] a start/stop time-varying covariate analysis was conducted, basically investigating current aspirin use, in which patients became aspirin users upon the date of each aspirin prescription, and remained aspirin users for the duration of the prescription at which point they became aspirin non-users. These analyses were conducted with no lag, a 6 month lag (accrual of person years at risk starts at 6 months after diagnosis and the dates of aspirin prescriptions were moved forward 6 months) and a 1 year lag (accrual of person years at risk starts at 1 years and the date of aspirin prescriptions were moved forward 1 year) as described above and were adjusted for the confounders mentioned previously. Supplementary Figure 1 contains diagrams illustrating these designs.

A separate sensitivity analysis was conducted to investigate the association between cancer-specific mortality and consistent aspirin use. A nested case-control design was used in which cases who died due to esophageal or gastric cancer were matched on age (in 5 year intervals), year of cancer diagnosis (in 1 year intervals), gender and site (esophageal or gastric cancer) to up to five esophageal or gastric cancer risk-set

controls who lived at least as long after their cancer diagnosis. The exposure period was from cancer diagnosis until 6 months prior to cancer-specific death in cases and for a period of identical duration from diagnosis in matched controls. Patients who died within 6 months of diagnosis were excluded. The number of aspirin tablets per day in the exposure period was determined and patients with greater than 0.8 (i.e. using over 80% of the time) were considered consistent aspirin users. Conditional logistic regression was then used to calculate odds ratios (ORs), and 95% CIs, for the association between consistent aspirin use and cancer-specific mortality, adjusting for treatment, deprivation, comorbidities and statin use.

## Results

### Patient cohorts

In the English cohort there were 11,044 gastroesophageal cancer patients. After exclusion criteria were applied, 2,733 esophageal cancer and 2,391 gastric cancer patients remained for analysis (Figure 1). The median follow up in England was 1.3 (minimum=0.5, maximum=17.2) years and 1.5 (minimum=0.5 years, maximum=17.2) years for esophageal and gastric cancer, respectively. There were 1,867 and 1,478 esophageal and gastric cancer-specific deaths in the English cohort, respectively. The Scottish cohort contained 1,921 esophageal and 1,442 gastric cancer patients (Figure 1). Mean follow up in this cohort was 1.3 years (minimum=0.5 years, maximum=6 years) for esophageal cancer patients and 1.6 years (minimum=0.5 years, maximum=6 years) for gastric cancer patients. There were 1,373 esophageal and 914 gastric cancer-specific deaths in the Scottish cohort.

### Patient Characteristics

Patient characteristics by aspirin use are shown for esophageal and gastric cancer patients in Tables 1 and 2, respectively. For both esophageal and gastric cancer cohorts, aspirin users, compared with non-users, were more likely to be male, older, have a history of comorbidities and use statins. Aspirin users in the gastric cancer cohort were slightly more likely to have surgery and radiotherapy, but less likely to have chemotherapy and higher grade tumors than non-users. Aspirin users in the esophageal cancer cohort were also more likely to undergo radiotherapy, and less likely to have chemotherapy, however the rates of surgery were similar when compared to non-users.

Association between aspirin use after diagnosis and survival

In esophageal cancer patients, the proportion surviving 1 year from the start of follow-up, based upon cancer-specific mortality, in aspirin users and non-users was 49% and 46% in Scotland and 48% and 50% in England, respectively. Similarly in gastric cancer patients, the proportion surviving 1 year in aspirin users versus non-users was 59% and 55% in Scotland and 58% versus 57% in England, respectively.

In esophageal and gastric cancer patients, there was little evidence of a reduction in cancer-specific mortality with any aspirin use compared with non-use before or after adjustment for confounders (pooled adjusted HR 0.98, 95% CI 0.89, 1.09 and adjusted HR 0.96, 95% CI 0.85, 1.08, respectively) (Table 3). These associations were similar in the Scottish and English cohorts. There was little evidence of a dose-response relationship; in esophageal and gastric cancer patients using more than 730 aspirin tablets the pooled adjusted HRs were 1.25, 95% CI 0.91, 1.71 and 1.12 95% CI 0.77, 1.64, respectively. Further analysis by histological subtype revealed no evidence of association in esophageal adenocarcinoma patients (pooled adjusted HR 1.05, 95% CI 0.93, 1.19), esophageal squamous cell carcinoma patients (pooled adjusted HR 0.89, 95% CI 0.74, 1.07) or gastric adenocarcinoma patients (pooled adjusted HR 0.92, 95% CI 0.81, 1.04), see Table 3.

Sensitivity analyses

Table 4 shows sensitivity analyses. In the majority of sensitivity analyses, the conclusions were little altered. In unlagged analysis for esophageal and gastric cancer, there was a slight reduction in cancer-specific mortality in aspirin users compared

with non-users (adjusted HR 0.87, 95% CI 0.81, 0.93 and adjusted HR 0.84, 95% CI 0.78, 0.92) but this was not apparent when a 3 month lag was used (adjusted HR 0.94, 95% CI 0.86, 1.02 and adjusted HR 0.93, 95% CI 0.84, 1.02) or when 6 or 12 month lags were used. Of particular note the associations for esophageal and gastric cancer were similar after additional adjustment for grade (pooled adjusted HR 1.01, 95% CI 0.90, 1.13 and adjusted HR 0.99, 95% CI 0.86, 1.13, respectively), stage and grade (adjusted HR 0.88, 95% CI 0.61, 1.27 and adjusted HR 1.25, 95% CI 0.71, 2.20, respectively), and smoking and BMI (adjusted HR 1.06, 95% CI 0.91, 1.24, adjusted HR 0.89, 95% CI 0.75, 1.05, respectively) in the English dataset. There was also little association when restricting the analysis to patients who underwent surgery (pooled adjusted HR 0.85, 95% CI 0.68, 1.05 and adjusted HR 1.00, 95% CI 0.82, 1.22, respectively) Also, there was no association between consistent aspirin use and esophageal or gastric cancer-specific mortality (pooled adjusted OR 0.92, 95% CI 0.79, 1.06 and adjusted OR 0.94, 95% CI 0.78, 1.13, respectively). For comparison with a previous study,[12;26] in separate start/stop time-varying covariate analyses, there was a marked protective effect of aspirin when no lag was applied (in esophageal and gastric cancer patients pooled adjusted HR 0.44, 95% CI 0.39, 0.49, and adjusted HR 0.46, 95% CI 0.41, 0.53, respectively), a slight protective effect when a 6 month lag was applied (pooled adjusted HR 0.87, 95% CI 0.77, 0.97, and adjusted HR 0.81, 95% CI 0.70, 0.94, respectively) and little evidence of association when a 12 month lag was applied (pooled adjusted HR 0.90, 95% CI 0.77, 1.06, and adjusted HR 0.99, 95% CI 0.82, 1.18, respectively).

Also, there was little association between aspirin use in the year preceding esophageal or gastric cancer diagnosis and mortality, compared with non-users (pooled adjusted HR 0.94, 95% CI 0.86, 1.02 and adjusted HR 0.95, 95% CI 0.88, 1.02, respectively).

## Discussion

In two large independent population-based cohorts of esophageal and gastric cancer patients we did not find any evidence that low-dose aspirin use reduced the risk of cancer-specific or all-cause mortality.

To date there have not been any previous studies investigating the impact of aspirin use on cancer-specific mortality in esophageal or gastric cancer patients. Only one observational study has investigated aspirin after diagnosis and all-cause mortality in gastric cancer patients, whilst three have investigated this association in esophageal cancer patients. A cohort study conducted in the Netherlands did not observe a statistically significant association (adjusted HR 0.87, 95% CI 0.47, 1.61) between current aspirin use after diagnosis and mortality in 750 gastric cancer patients[12] but did report a marked reduction in mortality in 560 esophageal cancer patients (adjusted HR 0.42, 95% CI 0.30, 0.57).[26] However it is possible that their analysis, which was of current aspirin use (using a start/stop time-varying covariate), could have led to reverse causation. Specifically, current aspirin users became aspirin non-users once their prescription was complete, therefore if medications were withdrawn from individuals who become terminally ill (as has been observed at other cancer sites[27]) then aspirin could artificially appear protective. Consistent with this bias, when we fitted models of current aspirin use (using a start/stop time-varying covariate) we observed similar marked protective effects, which seem implausible, and which were entirely attenuated once a year lag was used. In our main analysis we used a lag and once an individual became an aspirin user they remained an aspirin user, as seen in similar studies,[28;29] which reduces this potential bias.

A study based upon 2392 esophageal cancer patients from Scotland also observed a protective association for all-cause mortality in aspirin users after diagnosis (adjusted HR 0.54 95% CI 0.45, 0.64).[11] However, this protective association was attenuated in additional nested case-control analyses conducted to reduce immortal time bias, (OR 0.75, 95% CI 0.43, 1.31). Finally, a Chinese study of 1598 esophageal cancer patients observed a slight but significant reduction in 5 year mortality in low-dose aspirin users compared with non-users (relative risk 0.81).[13] However this study did not contain any dose response analyses, did not adjust for comorbidities and was conducted in a very specific cancer subset (undergoing resection for esophageal squamous cell carcinoma or gastric cardia adenocarcinoma). Our findings are similar to a recent US study which investigated aspirin use prior to esophageal cancer in 130 esophageal cancer patients, which found no association between medication use and cancer-specific mortality (HR 1.07 95% CI 0.52, 2.21),[30] however their study did not investigate aspirin use after diagnosis and had limited power.

Long term follow-up of randomised controlled trials of aspirin, designed with the primary aim to prevent vascular events, have detected reductions in the risk of death from esophageal and gastric cancer of around 50%,[8] and reductions in the risk of metastases after non-colorectal gastrointestinal cancer diagnosis by around 60%.[9] It is possible to speculate why we did not observe these protective effects: Firstly, the risk of death from cancer will reflect cancer incidence and it is plausible that aspirin could reduce esophageal and gastric cancer incidence but not improve survival. Similarly, as these trials were of aspirin treatment to reduce vascular events they were not specific to cancer patients and therefore all included individuals in the aspirin group were

taking aspirin for many years prior to cancer diagnosis. Finally, patients in these trials may have taken aspirin more regularly than patients in a real life setting,[31;32] but it is worth noting that our analyses of consistent aspirin use and long term aspirin use were also null.

At least one trial is ongoing investigating the effect of aspirin (both 100mg and 300mg) on survival in esophageal and gastric cancer patients.[14] This UK trial will provide more definitive evidence of the effect of low-dose aspirin in esophageal and gastric cancer patients, but a final report is not anticipated until 2027. Should further epidemiological studies observe null results in esophageal cancer patients this could inform the decision to conduct further trials and inform the interim analyses of this trial.

Strengths

The main strength of our study was the use of two large independent population-based cohorts, the long term follow-up (of up to 17 years), size (including 8,487 gastro-esophageal patients making this larger than all previous studies of aspirin on survival) and the ability to identify cancer-specific mortality which was not possible in previous studies investigating post-diagnostic aspirin use. We utilised high quality data from a number of sources (including English and Scottish cancer registries, and medication and national mortality records). Also, the use of routinely electronically updated databases eliminated the possibility of recall bias, a significant disadvantage of questionnaire-based studies.[33]

Limitations

We cannot exclude the effect of residual confounding from poorly measured or missing factors. In particular, stage was poorly recorded, although this is likely to bias our estimates toward a more protective effect as aspirin is less likely to be prescribed to patients with more advanced cancer (as seen in the Netherlands cohort in which 9% of stage four patients used aspirin compared with 24% of stage one patients).[12] Furthermore, our conclusions were unchanged in complete case and multiple imputation analyses adjusting for stage in the English cohort. We had limited information on smoking and BMI and only from the English cohort. Despite this, adjustments using complete case and imputation for esophageal and gastric cancer did not alter results. Additionally, misclassification of aspirin is possible as aspirin is available over-the-counter. However, a previous CPRD study estimated that 70% to 80% of aspirin use among middle-aged UK residents was prescription based,[34] whilst another showed little evidence of misclassification of aspirin usage by prescription records when compared with patient recall.[35] Also, a previous methodological study demonstrated that that valid treatment effects can be obtained where over-the-counter usage occurs particularly when medication use is around 35% and OTC use is under 30%, as seems likely in our study.[36] However, we cannot rule out the possibility of non-compliance. Furthermore, in other cancer sites, such as colorectal, aspirin has been shown to be protective only in particular molecular subtypes.[37] Molecular subtypes have only recently been identified for esophageal adenocarcinoma,[38] and as their association with prognosis is unknown it is too preliminary to investigate if stratified approaches by subtype are required. This may be, however, a component of future research.

## Conclusions

In conclusion, we found there was no significant reduction in mortality in esophageal or gastric cancer patients with low-dose aspirin use. Our findings do not support the conduct of further trials of low-dose aspirin in esophageal or gastric cancer patients.

## Acknowledgements

This study is based in part on data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the author/s alone. The authors would like to thank the research coordinators (Lizzie Nicholson and David Bailey) and NHS National Services Scotland for facilitating access and analysis of the Scottish cohort. This work was supported by a Clinical Research Bursary from Cancer Research-UK [C54914/A20558].

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136:E359-86.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015; 65:5-29.
3. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009; 373:1849-1860.
4. Bambace NM, Holmes CE. The platelet contribution to cancer progression. J Thromb Haemost 2011; 9:237-249.
5. Gasic GJ, Gasic TB, Stewart CC. Antimetastatic effects associated with platelet reduction. Proc Natl Acad Sci U S A 1968; 61:46-52.
6. Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011; 11:123-134.
7. Gasic GJ, Gasic TB, Murphy S. Anti-metastatic effect of aspirin. Lancet 1972; 2:932-933.
8. Rothwell PM, Fowkes FG, Belch JF, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011; 377:31-41.
9. Rothwell PM, Wilson M, Price JF, et al. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet 2012; 379:1591-1601.
10. Chubak J, Whitlock EP, Williams SB, et al. Aspirin for the Prevention of Cancer Incidence and Mortality: Systematic Evidence Reviews for the U.S. Preventive Services Task Force. Ann Intern Med 2016; 164:814-825.
11. Macfarlane TV, Murchie P, Watson MC. Aspirin and other non-steroidal anti-inflammatory drug prescriptions and survival after the diagnosis of head and neck and oesophageal cancer. Cancer Epidemiol 2015; 39:1015-1022.
12. Frouws MA, Bastiaannet E, Langley RE, et al. Effect of low-dose aspirin use on survival of patients with gastrointestinal malignancies; an observational study. Br J Cancer 2017; 116:405-413.

13. Liu JF, Jamieson GG, Wu TC, et al. A preliminary study on the postoperative survival of patients given aspirin after resection for squamous cell carcinoma of the esophagus or adenocarcinoma of the cardia. Ann Surg Oncol 2009; 16:1397-1402.
14. Coyle C, Cafferty FH, Rowley S, et al. ADD-ASPIRIN: A phase III, double-blind, placebo controlled, randomised trial assessing the effects of aspirin on disease recurrence and survival after primary therapy in common non-metastatic solid tumours. Contemp Clin Trials 2016; 51:56-64.
15. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015; 44:827-836.
16. World Health Organisation: World Health Organisation Collaborating Centre for Drug Statistics Methodology (http://www whocc no/ 2013). Accessed May 2017.
17. Khan NF, Perera R, Harper S, et al. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Fam Pract 2010; 11:1.
18. Sundararajan V, Henderson T, Perry C, et al. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. J Clin Epidemiol 2004; 57:1288-1294.
19. Scottish Government. Scottish Index of Multiple Deprivation 2009 Technical Report. Edinburgh: Scottish Government, 2009.
20. Levesque LE, Hanley JA, Kezouh A, et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ 2010; 340:b5087.
21. Chubak J, Boudreau DM, Wirtz HS, et al. Threats to Validity of Nonrandomized Studies of Postdiagnosis Exposures on Cancer Recurrence and Survival. J Natl Cancer Inst 2013; 105:1456-1462.
22. Sutton AJ, Abrams KR, Jones DR, et al. Methods for meta-analysis in medical research. Chichester: John Wiley & Sons Ltd, 2000.
23. Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus non-responder bias. Stat Med 1984; 3:35-44.
24. White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med 2009; 28:1982-1998.
25. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011; 30:377-399.

26. van Staalduinen J, Frouws M, Reimers M, et al. The effect of aspirin and nonsteroidal anti-inflammatory drug use after diagnosis on survival of oesophageal cancer patients. Br J Cancer 2016; 114:1053-1059.
27. Smith A, Murphy L, Bennett K, et al. Patterns of statin initiation and continuation in patients with breast or colorectal cancer, towards end-of-life. Support Care Cancer 2017; 25:1629-1637.
28. Yu O, Eberg M, Benayoun S, et al. Use of statins and the risk of death in patients with prostate cancer. J Clin Oncol 2014; 32:5-11.
29. Assayag J, Pollak MN, Azoulay L. The use of aspirin and the risk of mortality in patients with prostate cancer. J Urol 2015; 193:1220-1225.
30. Araujo JL, Altorki NK, Sonett JR, et al. Prediagnosis aspirin use and outcomes in a prospective cohort of esophageal cancer patients. Therap Adv Gastroenterol 2016; 9:806-814.
31. Jonasson G, Carlsen KH, Mowinckel P. Asthma drug adherence in a long term clinical trial. Arch Dis Child 2000; 83:330-333.
32. Ringdal N, Chuchalin A, Chovan L, et al. Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. Respir Med 2002; 96:851-861.
33. Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol 1990; 43:87-91.
34. Bedson J, Whitehurst T, Lewis M, et al. Factors affecting over-the-counter use of aspirin in the secondary prophylaxis of cardiovascular disease. Br J Gen Pract 2001; 51:1001-1003.
35. Yang YX, Hennessy S, Propert K, et al. Chronic statin therapy and the risk of colorectal cancer. Pharmacoepidemiol Drug Saf 2008; 17:869-876.
36. Yood MU, Campbell UB, Rothman KJ, et al. Using prescription claims data for drugs available over-the-counter (OTC). Pharmacoepidemiol Drug Saf 2007; 16:961-968.
37. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. N Engl J Med 2012; 367:1596-1606.

38. Secrier M, Li X, de Silva N, et al. Mutational signatures in esophageal adenocarcinoma define etiologically distinct subgroups with therapeutic relevance. Nat Genet 2016; 48:1131-1141.

Table 1. Characteristics of low-dose aspirin users and non-users after esophageal cancer diagnosis, restricted to participants living minimum 6 months after diagnosis.

| | English cohort | | Scottish cohort | |
|---|---|---|---|---|
| | **Aspirin non-user (2,174)** | **Aspirin user (559)** | **Aspirin non-user (1,436)** | **Aspirin user (485)** |
| Male | 1,430 (65.8%) | 412 (73.7%) | 928 (64.6%) | 343 (70.7%) |
| Year: 1998-2002 | 476 (21.9%) | 97 (17.4%) | | |
| 2003-2007 | 721 (33.2%) | 200 (35.8%) | | |
| 2008-2012 | 977 (44.9%) | 262 (46.9%) | 1,436 (100%) | 485 (100%) |
| Age: mean (SD) | 67.9 (11.8) | 72.7 (9.8) | 67.2 (11.4) | 72.4 (9.0) |
| <59 | 528 (24.3%) | 45 (8.1%) | 356 (24.8%) | 38 (7.8%) |
| 60-69 | 659 (30.3%) | 165 (29.5%) | 463 (32.2%) | 138 (28.5%) |
| 70-79 | 606 (27.9%) | 200 (35.8%) | 398 (27.7%) | 200 (41.2%) |
| 80+ | 381 (17.5%) | 149 (26.7%) | 219 (15.3%) | 109 (22.5%) |
| Grade: 1 | 87 (4.0%) | 24 (4.3%) | 30 (2.1%) | 7 (1.4%) |
| 2 | 725 (33.3%) | 190 (34.0%) | 454 (31.6%) | 177 (36.5%) |
| 3-4 | 817 (37.6%) | 198 (35.4%) | 686 (47.8%) | 197 (40.6%) |
| Missing | 545 (25.1%) | 147 (26.3%) | 266 (18.5%) | 104 (21.4%) |
| Histology: Adenocarcinoma | 1,256 (57.8%) | 349 (62.4%) | 882 (61.4%) | 296 (61.0%) |
| Squamous | 678 (31.2%) | 152 (27.2%) | 502 (35.0%) | 165 (34.0%) |
| Other/unknown | 240 (11.0%) | 58 (10.4%) | 52 (3.6%) | 24 (4.9%) |
| Treatment[a,b]: Surgery | 879 (40.4%) | 215 (38.5%) | 266 (18.5%) | 90 (18.6%) |
| Chemotherapy | 1,087 (50.0%) | 235 (42.0%) | 883 (61.5%) | 256 (52.8%) |
| Radiotherapy | 550 (25.3%) | 158 (28.3%) | 424 (29.5%) | 188 (38.8%) |
| Deprivation: 1 (Least Deprived) | 455 (20.9%) | 116 (20.8%) | 252 (17.5%) | 66 (13.6%) |
| 2 | 554 (25.5%) | 141 (25.2%) | 274 (19.1%) | 94 (19.4%) |
| 3 | 435 (20.0%) | 110 (19.7%) | 303 (21.1%) | 99 (20.4%) |
| 4 | 412 (19.0%) | 109 (19.5%) | 286 (19.9%) | 105 (21.6%) |
| 5 (Most Deprived) | 317 (14.6%) | 83 (14.8%) | 321 (22.4%) | 121 (24.9%) |
| Comorbidity[c] | | | | |
| Chronic pulmonary disease | 255 (11.7%) | 77 (13.8%) | 111 (7.7%) | 78 (16.1%) |
| Diabetes | 210 (9.7%) | 114 (20.4%) | 67 (4.7%) | 66 (13.6%) |
| Renal disease | 153 (7.0%) | 71 (12.7%) | 25 (5.2%) | 27 (1.9%) |
| Cerebrovascular disease | 72 (3.3%) | 62 (11.1%) | 57 (4.0%) | 42 (8.7%) |
| Peripheral vascular disease | 56 (2.6%) | 55 (9.8%) | 38 (2.6%) | 29 (6.0%) |
| Myocardial infarction | 28 (1.3%) | 62 (11.1%) | 40 (2.8%) | 62 (12.8%) |
| Congestive heart disease | 64 (2.9%) | 31 (5.5%) | 41 (2.9%) | 44 (9.1%) |
| Peptic ulcer disease | 47 (2.2%) | 8 (1.4%) | 57 (4.0%) | 22 (4.5%) |
| Statin use (after diagnosis) | 345 (15.9%) | 350 (62.6%) | 288 (20.1%) | 363 (74.8%) |
| Stage[d]: 1 | 34 (1.6%) | 10 (1.8%) | | |
| 2 | 69 (3.2%) | 28 (5.0%) | | |
| 3 | 183 (8.4%) | 47 (8.4%) | | |
| 4 | 132 (6.1%) | 23 (4.1%) | | |
| Missing | 1,756 (80.8%) | 451 (80.7%) | | |
| Smoking[d]: Current | 542 (24.9%) | 99 (17.7%) | | |
| Ex | 654 (30.1%) | 250 (44.7%) | | |
| Non-smoker | 787 (36.2%) | 179 (32.0%) | | |
| Missing | 191 (8.8%) | 31 (5.6%) | | |
| BMI[d]: mean (SD) | 26.5 (5.1) | 27.6 (5.7) | | |

[a]In first 6 months
[b]Patients may have had more than one type of treatment
[c]Before diagnosis
[d]Data not reported for Scotland cohort

Table 2. Characteristics of low-dose aspirin users and non-users after gastric cancer diagnosis, restricted to participants living minimum 6 months after diagnosis.

| | English cohort | | Scottish cohort | |
|---|---|---|---|---|
| | **Aspirin non-user (1,895)** | **Aspirin user (496)** | **Aspirin non-user (1,130)** | **Aspirin user (312)** |
| Male | 1,249 (65.9%) | 368 (74.2%) | 696 (61.6%) | 226 (72.4%) |
| Year: 1998-2002 | 516 (27.2%) | 112 (22.6%) | | |
| 2003-2007 | 669 (35.3%) | 181 (36.5%) | | |
| 2008-2012 | 710 (37.5%) | 203 (40.9%) | 1,130 (100%) | 312 (100%) |
| Age: mean (SD) | 69.6 (12.4) | 73.9 (9.1) | 69.1 (12.4) | 72.3 (9.2%) |
| <60 | 382 (20.1%) | 33 (6.6%) | 243 (21.5%) | 24 (7.7%) |
| 60-69 | 452 (23.9%) | 112 (22.6%) | 727 (28.3%) | 218 (27.4%) |
| 70-79 | 637 (33.6%) | 218 (44.0%) | 785 (30.6%) | 341 (42.8%) |
| 80+ | 424 (22.4%) | 133 (26.8%) | 455 (17.7%) | 176 (22.1%) |
| Grade: 1 | 65 (3.4%) | 22 (4.4%) | 43 (3.8%) | 9 (2.9%) |
| 2 | 448 (23.6%) | 144 (29.0%) | 233 (20.6%) | 81 (26.0%) |
| 3-4 | 874 (46.1%) | 177 (35.7%) | 603 (53.4%) | 158 (50.6%) |
| Missing | 508 (26.8) | 153 (30.8%) | 251 (22.2%) | 64 (20.5%) |
| Histology: Adenocarcinoma | 1,516 (80.0%) | 419 (84.5%) | 1005 (88.9%) | 290 (92.9%) |
| Squamous | 18 (1.0%) | 1 (0.2%) | 14 (1.2%) | 0 (0.0%) |
| Other/unknown | 360 (19.0%) | 76 (15.3%) | 111 (9.8%) | 22 (7.1%) |
| Treatment[a,b]: Surgery | 947 (50.0%) | 273 (55.0%) | 376 (33.3%) | 124 (39.7%) |
| Chemotherapy | 720 (38.0%) | 146 (29.4%) | 587 (51.9%) | 145 (46.5%) |
| Radiotherapy | 123 (6.5%) | 38 (7.7%) | 68 (6.0%) | 13 (4.2%) |
| Deprivation: 1 (Least Deprived) | 361 (19.1%) | 91 (18.4%) | 206 (18.2%) | 38 (12.2%) |
| 2 | 465 (24.6%) | 112 (22.6%) | 218 (19.3%) | 47 (15.1%) |
| 3 | 376 (19.9%) | 101 (20.4%) | 208 (18.4%) | 67 (21.5%) |
| 4 | 400 (21.1%) | 112 (22.6%) | 273 (24.2%) | 83 (26.6%) |
| 5 (Most Deprived) | 291 (15.4%) | 79 (16.0%) | 225 (19.9%) | 77 (24.7%) |
| Comorbidity[c] | | | | |
| Chronic pulmonary disease | 225 (11.9%) | 72 (14.5%) | 97 (8.6%) | 35 (11.2%) |
| Diabetes | 202 (10.7%) | 110 (22.2%) | 91 (8.1%) | 55 (17.6%) |
| Renal disease | 126 (6.6%) | 62 (12.5%) | 25 (2.2%) | 14 (4.5%) |
| Cerebrovascular disease | 75 (4.0%) | 51 (10.3%) | 53 (4.7%) | 45 (14.4%) |
| Peripheral vascular disease | 81 (4.3%) | 51 (10.3%) | 34 (3.0%) | 28 (9.0%) |
| Myocardial infarction | 60 (3.2%) | 48 (9.7%) | 47 (4.2%) | 46 (14.7%) |
| Congestive heart disease | 72 (3.8%) | 31 (6.3%) | 24 (2.1%) | 25 (8.0%) |
| Peptic ulcer disease | 146 (7.7%) | 48 (9.7%) | 139 (12.3%) | 31 (9.9%) |
| Statin use (after diagnosis) | 346 (18.3%) | 306 (61.7%) | 303 (26.8%) | 233 (74.7%) |
| Stage[d]: 1 | 28 (1.5%) | 12 (2.4%) | | |
| 2 | 43 (2.3%) | 20 (4.0%) | | |
| 3 | 59 (3.1%) | 16 (3.2%) | | |
| 4 | 119 (6.3%) | 16 (3.2%) | | |
| Missing | 1,646 (86.9%) | 432 (87.1%) | | |
| Smoking[d]: Current | 367 (19.4%) | 91 (18.3%) | | |
| Ex | 610 (32.2%) | 205 (41.3%) | | |
| Non-smoker | 722 (38.1%) | 174 (35.1%) | | |
| Missing | 196 (10.3%) | 26 (5.2%) | | |
| BMI[d]: mean (SD) | 26.4 (4.9) | 26.7 (4.6) | | |

[a]In first 6 months
[b]Patients may have had more than one type of treatment
[c]Before diagnosis
[d]Data not reported for Scotland cohort

Table 3: Association between low-dose aspirin use and esophageal and gastric cancer death

| | English cohort | | | | | Scottish cohort | | | | | Pooled | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients | Person years | Cancer-deaths | Unadjusted HR (95% CI) | Adjusted HR[a] (95% CI) | Patients | Person years | Cancer-deaths | Unadjusted HR (95% CI) | Adjusted HR[a] (95% CI) | Adjusted HR[b] (95%CI) | Test for trend p-value[c] |
| **Esophageal** | | | | | | | | | | | | |
| Non-user | 2,174 | 3,821 | 1,527 | 1.00 (Ref.) | 1.00 (Ref.) | 1,436 | 1,920 | 1,054 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | |
| User | 559 | 1,016 | 340 | 1.05 (0.93,1.18) | 1.01 (0.88,1.17) | 485 | 631 | 319 | 1.00 (0.88,1.14) | 0.95 (0.82,1.10) | 0.98 (0.89,1.09) | |
| < 365 tablets | 386 | 571 | 271 | 1.06 (0.93,1.21) | 1.04 (0.90,1.20) | 316 | 412 | 247 | 0.96 (0.83,1.10) | 0.91 (0.77,1.07) | 0.98 (0.88,1.09) | 0.88 |
| ≥ 365 tablets | 173 | 446 | 69 | 1.00 (0.78,1.28) | 0.92 (0.70,1.20) | 169 | 219 | 72 | 1.21 (0.94,1.57) | 1.15 (0.88,1.50) | 1.03 (0.85,1.25) | |
| 1-182 tablets | 284 | 409 | 206 | 1.07 (0.93,1.24) | 1.05 (0.90,1.23) | 239 | 277 | 193 | 1.02 (0.88,1.20) | 0.97 (0.82,1.16) | 1.01 (0.90,1.14) | |
| 183-364 tablets | 102 | 162 | 65 | 1.03 (0.80,1.33) | 0.99 (0.76,1.29) | 77 | 135 | 54 | 0.77 (0.58,1.02) | 0.73 (0.54,0.98) | 0.87 (0.71,1.06) | |
| 365-547 tablets | 36 | 94 | 20 | 0.74 (0.48,1.16) | 0.72 (0.46,1.13) | 40 | 77 | 33 | 1.12 (0.78,1.60) | 1.06 (0.73,1.53) | 0.91 (0.68,1.21) | 0.97 |
| 548-729 tablets | 43 | 78 | 22 | 1.26 (0.82,1.94) | 1.15 (0.74,1.79) | 57 | 73 | 20 | 1.00 (0.63,1.59) | 0.94 (0.59,1.49) | 1.05 (0.76,1.44) | |
| ≥ 730 tablets | 94 | 273 | 27 | 1.11 (0.74,1.65) | 0.97 (0.64,1.46) | 72 | 69 | 19 | 1.89 (1.15,3.10) | 1.80 (1.09,2.97) | 1.25 (0.91,1.71) | |
| **Esophageal adenocarcinoma** | | | | | | | | | | | | |
| Non-user | 1,256 | 2,326 | 881 | 1.00 (Ref.) | 1.00 (Ref.) | 882 | 1,211 | 644 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | |
| User | 349 | 661 | 216 | 1.06 (0.92,1.24) | 1.10 (0.92,1.31) | 296 | 397 | 194 | 1.00 (0.85,1.17) | 1.00 (0.83,1.21) | 1.05 (0.93,1.19) | |
| **Esophageal squamous cell carcinoma** | | | | | | | | | | | | |
| Non-user | 678 | 1,084 | 474 | 1.00 (Ref.) | 1.00 (Ref.) | 502 | 645 | 375 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | |
| User | 152 | 256 | 92 | 1.05 (0.84,1.32) | 0.90 (0.70,1.17) | 165 | 201 | 110 | 1.03 (0.83,1.27) | 0.88 (0.68,1.14) | 0.89 (0.74,1.07) | |
| **Gastric** | | | | | | | | | | | | |
| Non-user | 1,895 | 4,069 | 1,244 | 1.00 (Ref.) | 1.00 (Ref.) | 1,130 | 1,829 | 736 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | |
| User | 496 | 1,121 | 234 | 0.93 (0.80,1.07) | 0.95 (0.82,1.11) | 312 | 493 | 178 | 1.00 (0.84,1.18) | 0.97 (0.80,1.17) | 0.96 (0.85,1.08) | |
| < 365 tablets | 300 | 595 | 179 | 0.92 (0.79,1.08) | 0.94 (0.79,1.11) | 199 | 324 | 138 | 0.96 (0.80,1.16) | 0.93 (0.76,1.14) | 0.94 (0.82,1.07) | 0.82 |
| ≥ 365 tablets | 196 | 526 | 55 | 0.94 (0.71,1.24) | 1.01 (0.76,1.35) | 113 | 169 | 40 | 1.13 (0.81,1.58) | 1.13 (0.80,1.59) | 1.06 (0.85,1.32) | |
| 1-182 tablets | 226 | 432 | 139 | 0.96 (0.80,1.14) | 0.98 (0.81,1.18) | 139 | 223 | 91 | 0.88 (0.71,1.10) | 0.85 (0.67,1.08) | 0.93 (0.80, 1.08) | |
| 183-364 tablets | 74 | 163 | 40 | 0.82 (0.60,1.13) | 0.82 (0.59,1.14) | 60 | 101 | 47 | 1.18 (0.87,1.60) | 1.16 (0.84,1.59) | 0.98 (0.78, 1.23) | |
| 365-547 tablets | 45 | 102 | 18 | 0.78 (0.49,1.26) | 0.81 (0.50,1.30) | 26 | 61 | 15 | 0.89 (0.53,1.50) | 0.87 (0.51,1.47) | 0.84 (0.59, 1.19) | 0.76 |
| 548-729 tablets | 48 | 88 | 17 | 1.21 (0.74,1.97) | 1.36 (0.83,2.23) | 29 | 47 | 14 | 1.46 (0.84,2.52) | 1.51 (0.87,2.63) | 1.43 (0.99, 2.06) | |
| ≥ 730 tablets | 103 | 336 | 20 | 0.92 (0.58,1.47) | 1.03 (0.64,1.65) | 58 | 62 | 11 | 1.30 (0.70,2.42) | 1.30 (0.69,2.44) | 1.12 (0.77. 1.64) | |
| **Gastric adenocarcinoma** | | | | | | | | | | | | |
| Non-user | 1,516 | 3,161 | 1,022 | 1.00 (Ref.) | 1.00 (Ref.) | 1,005 | 1,565 | 685 | 1.00 (Ref.) | 1.00 (Ref.) | 1.00 (Ref.) | |
| User | 419 | 934 | 202 | 0.89 (0.77,1.04) | 0.92 (0.78,1.09) | 290 | 447 | 168 | 0.94 (0.79,1.12) | 0.92 (0.76,1.12) | 0.92 (0.81,1.04) | |

[a]Model contains sex, age, year of diagnosis, deprivation, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and other prescription medication use (aspirin and statin use, as time varying covariates)
[b]Pooled results of both English and Scottish cohorts.
[c]Test for trend per category increase pooled across the English and Scottish cohorts.

Table 4. Sensitivity analyses of association between aspirin use and cancer-specific and all-cause mortality for both cohorts.

| | English cohort | | | | Scottish cohort | | | | Pooled |
|---|---|---|---|---|---|---|---|---|---|
| | Cancer-specific deaths | Person years | Unadjusted HR (95% CI) | Adjusted HR[a] (95% CI) | Cancer-specific deaths | Person years | Unadjusted HR (95% CI) | Adjusted HR[b] (95% CI) | Adjusted HR[c] (95%CI) |
| **Esophageal** | | | | | | | | | |
| Main analysis (ever use)[b] | 1,867 | 4,837 | 1.05 (0.93,1.18) | 1.01 (0.88,1.17) | 1,373 | 2,551 | 1.00 (0.88,1.14) | 0.95 (0.82,1.10) | 0.98 (0.89,1.09) |
| No exposure lag | 3,581 | 6,629 | 0.96 (0.88,1.05) | 0.83 (0.75,0.91) | 2,385 | 3,765 | 0.89 (0.81,0.98) | 0.92 (0.82,1.02) | 0.87 (0.81, 0.93) |
| Exposure lag of 3 months | 2,538 | 5,608 | 0.98 (0.89, 1.09) | 0.90 (0.80, 1.01) | 1,794 | 3,087 | 0.99 (0.89, 1.11) | 0.98 (0.87, 1.12) | 0.94 (0.86, 1.02) |
| Exposure lag of 1 year | 1,001 | 3,744 | 0.96 (0.82,1.14) | 0.90 (0.74,1.09) | 697 | 1,784 | 1.07 (0.89,1.27) | 1.06 (0.86,1.30) | 0.97 (0.84,1.12) |
| Simplified first 6 month analysis[c] | 1,867 | 4,837 | 1.02 (0.90,1.15) | 0.98 (0.86,1.13) | 1,373 | 2,551 | 0.95 (0.84, 1.08) | 0.92 (0.79,1.06) | 0.95 (0.86,1.05) |
| Restricted to non-aspirin user prior[d] | 1,425 | 3,890 | 0.89 (0.67,1.18) | 0.85 (0.64,1.14) | 725 | 1,314 | 1.20 (0.87,1.67) | 1.02 (0.72,1.45) | 0.92 (0.73,1.14) |
| Restricted to aspirin user prior[e] | 442 | 947 | 1.07 (0.87,1.32) | 1.19 (0.95,1.49) | 291 | 488 | 0.80 (0.61,1.04) | 0.76 (0.57,1.02) | 1.01 (0.84,1.20) |
| Adjusting for aspirin in year prior[f] | 1,867 | 4,837 | 1.05 (0.93,1.18) | 1.03 (0.88,1.22) | 1,016 | 1,802 | 1.01 (0.87,1.17) | 0.89 (0.72,1.11) | 0.98 (0.86, 1.11) |
| In patients undergoing surgery[g] | 657 | 2,733 | 0.95 (0.77,1.17) | 0.81 (0.63,1.03) | 151 | 821 | 0.99 (0.67,1.47) | 1.01 (0.61,1.67) | 0.85 (0.68,1.05) |
| In statin users[h] | 398 | 1,401 | 1.04 (0.85,1.27) | 0.98 (0.79,1.21) | 425 | 874 | 0.98 (0.81, 1.18) | 0.99 (0.81, 1.20) | 0.99 (0.85, 1.14) |
| In statin non-users[i] | 1,469 | 3,436 | 1.31 (1.10,1.56) | 1.07 (0.89,1.28) | 948 | 1,677 | 1.09 (0.88, 1.36) | 0.89 (0.70, 1.13) | 1.00 (0.87, 1.16) |
| Consistent aspirin users v non-users[j] | 1,867 | | 0.95 (0.79,1.15) | 0.96 (0.78,1.18) | 1,350 | | 0.89 (0.73, 1.08) | 0.89 (0.68, 1.04) | 0.92 (0.79,1.06) |
| All-cause mortality[k] | 2,051 | 4,837 | 1.13 (1.01,1.26) | 1.06 (0.93,1.21) | 1,502 | 2,551 | 1.09 (0.96,1.22) | 1.00 (0.87,1.15) | 1.03 (0.93,1.13) |
| Aspirin use prior[l] | 3,581 | 6,629 | 1.11 (1.03,1.20) | 0.94 (0.86,1.03) | 1,798 | 2,720 | 1.13 (1.02,1.25) | 0.95 (0.85,1.08) | 0.94 (0.88,1.01) |
| Adjusting for grade[m] | 1,411 | 3,466 | 1.07 (0.93,1.22) | 1.07 (0.91,1.25) | 1,117 | 2,063 | 1.02 (0.89,1.18) | 0.94 (0.80,1.11) | 1.01 (0.90,1.13) |
| Adjusting for stage and grade[n§] | 281 | 615 | 0.96 (0.71,1.29) | 0.88 (0.61,1.27) | | | | | |
| Adjusting for stage and grade (MI)[o§] | 1,867 | 4,837 | 1.05 (0.93,1.18) | 1.00 (0.85,1.17) | | | | | |
| Adjusting for smoking & obesity[p§] | 1,444 | 3,864 | 1.08 (0.95,1.23) | 1.06 (0.91,1.24) | | | | | |
| Adjusting for smoking & obesity (MI)[q§] | 1,867 | 4,837 | 1.05 (0.93,1.18) | 1.02 (0.89,1.17) | | | | | |
| **Gastric** | | | | | | | | | |
| Main analysis (ever use)[b] | 1,478 | 5,190 | 0.93 (0.80,1.07) | 0.95 (0.82,1.11) | 914 | 2,322 | 1.00 (0.84,1.18) | 0.97 (0.80,1.17) | 0.96 (0.84,1.07) |
| No exposure lag | 3,213 | 6,758 | 0.84 (0.76,0.94) | 0.79 (0.71,0.88) | 1,902 | 3,264 | 0.88 (0.77,0.99) | 0.93 (0.82,1.07) | 0.84 (0.78, 0.92) |
| Exposure lag of 3 months | 2,024 | 5,854 | 0.90 (0.80, 1.02) | 0.88 (0.78, 1.01) | 1,241 | 2,725 | 0.98 (0.85, 1.13) | 1.00 (0.85, 1.17) | 0.93 (0.84, 1.02) |
| Exposure lag of 1 year | 815 | 4,200 | 0.89 (0.73,1.07) | 0.88 (0.72,1.09) | 527 | 1,717 | 1.13 (0.92,1.40) | 1.02 (0.80,1.31) | 0.94 (0.80,1.10) |
| Simplified first 6 month analysis[c] | 1,478 | 5,190 | 0.91 (0.79,1.05) | 0.94 (0.81,1.09) | 914 | 2,322 | 0.96 (0.82,1.13) | 0.98 (0.82,1.18) | 0.96 (0.85,1.07) |
| Restricted to non-aspirin user prior[d] | 1,093 | 3,931 | 1.06 (0.80,1.40) | 1.01 (0.76,1.36) | 456 | 1,122 | 1.19 (0.79,1.80) | 1.04 (0.68,1.60) | 1.02 (0.80,1.30) |
| Restricted to aspirin user prior[e] | 385 | 1,259 | 0.79 (0.64,0.97) | 0.84 (0.68,1.05) | 205 | 464 | 0.92 (0.70,1.23) | 0.96 (0.71,1.30) | 0.88 (0.74,1.05) |
| Adjusting for aspirin in year prior[f] | 1,478 | 5,190 | 0.93 (0.80,1.07) | 0.94 (0.79,1.11) | 661 | 1,586 | 1.03 (0.85,1.25) | 0.98 (0.77,1.24) | 0.95 (0.83 1.10) |
| In patients undergoing surgery[g] | 647 | 3,611 | 0.89 (0.72,1.10) | 0.94 (0.74,1.20) | 214 | 1,122 | 1.26 (0.92,1.72) | 1.15 (0.80,1.65) | 1.00 (0.82,1.22) |
| In statin users[h] | 313 | 1,456 | 0.95 (0.75,1.19) | 0.93 (0.74,1.18) | 301 | 865 | 0.96 (0.76, 1.20) | 0.88 (0.69, 1.11) | 0.91 (0.77, 1.07) |
| In statin non-users[i] | 1,165 | 3,735 | 1.05 (0.85,1.29) | 0.95 (0.77,1.17) | 613 | 1,457 | 1.23 (0.92, 1.63) | 1.16 (0.86, 1.55) | 1.02 (0.86, 1.21) |
| Consistent aspirin users v non-users[j] | 1,478 | | 0.85 (0.67,1.08) | 0.97 (0.75,1.25) | 896 | | 0.90 (0.70, 1.16) | 0.90 (0.72, 1.25) | 0.94 (0.78,1.13) |
| All-cause mortality[k] | 1,768 | 5,190 | 1.04 (0.92,1.18) | 1.00 (0.88,1.15) | 1,008 | 2,322 | 1.08 (0.92,1.26) | 1.02 (0.86,1.22) | 1.01 (0.90,1.12) |
| Aspirin use prior[l] | 3,213 | 6,758 | 1.02 (0.94,1.10) | 0.95 (0.87,1.04) | 1,399 | 2,283 | 1.05 (0.94,1.18) | 0.94 (0.83,1.07) | 0.95 (0.88,1.02) |
| Adjusting for grade[m] | 1,086 | 3,745 | 0.89 (0.76,1.06) | 0.99 (0.82,1.19) | 738 | 1,759 | 0.99 (0.82,1.19) | 1.00 (0.81,1.23) | 0.99 (0.86,1.13) |
| Adjusting for stage and grade[n§] | 141 | 388 | 1.00 (0.63,1.58) | 1.25 (0.71,2.20) | | | | | |
| Adjusting for stage and grade (MI)[o§] | 1,478 | 5,190 | 0.93 (0.80,1.07) | 0.98 (0.83,1.15) | | | | | |
| Adjusting for smoking & obesity[p§] | 1,141 | 4,038 | 0.89 (0.76,1.03) | 0.89 (0.75,1.05) | | | | | |
| Adjusting for smoking & obesity (MI)[q§] | 1,478 | 5,190 | 0.93 (0.80,1.07) | 0.95 (0.81,1.11) | | | | | |

[a]Except where otherwise stated model contains sex, age, year of diagnosis, deprivation, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and other prescription medication use (aspirin and statin use, as time varying covariates).
[b]Analysis undertaken applying a lag of 6 months.
[c]Analysis comparing aspirin users in the 6 months after diagnosis to aspirin non-users in the 6 months after diagnosis.
[d]Analysis of aspirin users after diagnosis compared with aspirin non-users after diagnosis restricted to aspirin non-users in the year prior to diagnosis, restricted to diagnoses after 2009 in Scotland as a full year of prescriptions records not available prior to this time.
[e]Analysis of aspirin users after diagnosis compared with aspirin non-users after diagnosis restricted to aspirin users in the year prior to diagnosis, restricted to diagnoses after 2009 in Scotland as a full year of prescriptions records not available prior to this time.
[f]Analysis of aspirin users after diagnosis compared with aspirin non-users after diagnosis adjusting for aspirin use in the year prior to diagnosis, restricted to diagnoses after 2009 in Scotland as a full year of prescriptions records not available prior to this time.
[g]Restricted to patients undergoing surgery.
[h]Analysis of aspirin users after diagnosis compared with aspirin non-users after diagnosis restricted to statin users after diagnosis.
[i]Analysis of aspirin users after diagnosis compared with aspirin non-users after diagnosis restricted to statin non-users after diagnosis.
[j]Case-control analysis comparing consistent aspirin users to non-users, accounting for age, gender and year in the matched design and adjusting for treatment, deprivation, comorbidities and statin use. In Scotland and England, 11% (144/1,350) and 8.4% (156/1,867) of cancer-specific deaths and 12% (781/6443) and 8.7% (675/7,769) of controls were consistent aspirin users in esophageal cancer patients. Similarly, 9% (82/896) and 6.4% (94/1,478) of cancer-specific deaths and 10% (433/4266) and 7.5% (461/6,164) of controls were consistent aspirin users in gastric cancer patients.
[k]Analysis of all-cause mortality.
[l]Aspirin users compared with non–users in year prior to diagnosis, restricted to diagnoses after 2009 in Scotland as a full year of prescriptions records not available prior to this time.
[m]Adjusting for grade using complete case analysis.
[n]Adjusting for stage and grade using complete case analysis.
[o]Adjusting for stage and grade using multiple imputation analysis.
[p]Adjusting for smoking history and obesity using complete case analysis, not conducted in Scottish cohort as stage and lifestyle data not available.
[q]Adjusting for smoking history and obesity using multiple imputation analysis, not conducted in Scottish cohort as stage and lifestyle data not available.
[§]Data not available for Scotland cohort.

## Figure legend

Figure 1: Study flow diagram for the England and Scotland datasets showing the eligibility process for esophageal and gastric cancer patients

Supplementary Figure 1: Figure illustrating the study design for the